UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,758	02/27/2004	Joseph Cohen	B45187 C1	1891

7590 05/03/2007

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939

EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
05/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,758	COHEN ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 22, 2006 has been entered.

2. Applicants' amendment filed December 22, 2006 is acknowledged and has been entered. Claims 1-15, 21, 23 and 24 have been canceled. Claims 16-20 have been amended. Claims 16-20 and 22 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 16-20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoute et al (New England J. Medicine, January, 1997, 336:86-91) taken with Davis et al 6406705.

Stoute et al teaches a recombinant vaccine based on fusion of the circumsporozoite protein and HBsAg (RTS,S) plus a potent adjuvant can protect against experimental challenge with *P. falciparum* sporozoites. After additional studies of protective immunity and the vaccination schedule, field trials are

indicated for this new vaccine against *P. falciparum* malaria (Conclusion, p. 86; pp. 88-89). Stoute et al teaches a vaccine formulation comprising the RTS,S and two adjuvants, aluminum salt and monophosphoryl lipid A (p. 87). Stoute et al teaches the development of an immunogenic recombinant circumsporozoite vaccine that protects adults who have never been exposed to malaria against experimental challenge with *P. falciparum* sporozoites (p. 90). "Complete immunity against infection rarely develops from natural exposure, but immunization with radiation-attenuated sporozoites affords full protection. This vaccine strategy is not practical, since it requires repeated exposure to hundreds of infected, irradiated mosquitoes over a period of 6 to 10 months, and sporozoites cannot be cultured in vitro. Nonetheless, these findings revealed a critical role for the circumsporozoite protein in the development of immunity against sporozoite challenge and led to its development as a candidate vaccine. In clinical trials, however, the circum-sporozoite protein is poorly immunogenic, and few subjects have been protected. To address these issues, we created a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) was expressed together with unfused HBsAg. The resulting hybrid was significantly more potent than previous circum-sporozoite-protein formulations. We hypothesized that more potent adjuvants could improve the efficacy of the vaccine. We therefore conducted a clinical trial to determine the safety and efficacy of three formulations of circumsporozoite protein vaccines against *P. falciparum.*" (p. 86) Stoute et al teaches the claimed invention except for the use of immunostimulatory CpG oligonucleotides.

However, Davis et al teaches compositions comprising synergistic adjuvants (CpG and non-nucleic acid adjuvant) and antigen (abstract; claims). The antigen

can be a parasite antigen (i.e. malarial antigen) (see col. 2; col. 16). The non-nucleic acid adjuvant can be MPL (col. 4; col. 14). Davis et al teaches that the oligonucleotide size can be 8 to 100 nucleotides, preferably 8 to 40 nucleotides (col. 4; col. 11). The prior art specifically teaches the immunostimulatory CpG oligonucleotides as set forth in claim 20. SEQ ID NO: 1, 2 and 6 are identical to SEQ ID NO: 86/90, 51 and 86/90 respectively (see attached sequence search printout). Davis et al teaches that the composition comprise a "...synergistic combination of adjuvants. The composition includes an effective amount for inducing a synergistic adjuvant response of a combination of adjuvants, wherein the combination of adjuvants includes at least one oligonucleotide containing at least one unmethylated CpG dinucleotide and at least one non-nucleic acid adjuvant. The composition may also include at least one antigen, which may be selected from the group consisting of peptides, polypeptides, cells, cell extracts, polysaccharides, polysaccharide conjugates, lipids, glycolipids and carbohydrates. Antigens may be given in a crude, purified or recombinant form and polypeptide/ peptide antigens, including peptide mimics of polysaccharides, may also be encoded within nucleic acids. Antigens may be derived from an infectious pathogen such as a virus, bacterium, fungus or parasite, or the antigen may be a tumor antigen, or the antigen may be an allergen." (col. 3) "In addition to the use of the combination of adjuvants for prophylactic treatment, the invention also encompasses the use of the combination for the immunotherapeutic treatment of a subject having an infection, an allergy or a cancer. A "subject having an infection" is a subject that has been exposed to an infectious pathogen and has acute or chronic detectable levels of the pathogen in the body. The combination of adjuvants can be used with an antigen to mount an antigen specific immune

response that is capable of reducing the level of or eradicating the infectious pathogen. An infectious disease, as used herein, is a disease arising from the presence of a foreign microorganism in the body." (col. 8) It would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare a composition comprising the RTS,S and adjuvant (CpG or CpG and aluminum salts) since the prior art teaches that the RTS,S was a better vaccine composition when a combination of adjuvants were present. Further, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the CpG adjuvant in a vaccine composition for administration to a human since the art teaches that the CpG is a potent adjuvant and that it induces a Th1-type immune response, including Th1 cytokines such as IL-12 and interferon gamma for protection against various pathogens including parasites. It would have been obvious to a person of ordinary skill in the art at the time the invention was made that there would be a reasonable expectation of success of preventing or ameliorating plasmodium infection in a patient if the prepared composition taught by Stoute et al taken with Davis et al were administered to the patient. Absent any convincing or unexpected evidence to the contrary, the claimed invention is prima facie obvious in view of the combined teachings of the prior art.

Applicant's arguments filed December 22, 2006 have been fully considered but they are not persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., humoral and cell-mediated immune responses; improved immunogenicity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the

specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is noted that the Examiner is not suggesting that Applicants amend the claims to recite these limitations.

Applicants have asserted that Stoute et al does not teach the particular claimed formulation, which combines the RTS,S or RTS,S* antigens with a combination of CpG and alum adjuvants. However it is noted that this 103 obviousness rejection is over Stoute et al taken with Davis et al, not Stoute et al alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants have asserted that generalized statements from Davis et al do not suggest the specific malarial antigens and formulations currently claimed. "For example, Davis provides experimental evidence suggesting that a single dose of recombinant HBsAg antigen in combination with a CpG oligonucleotide adjuvant yields an antibody titer 60-fold higher than preimmune serum. (column 37, line 13). In contrast, Fig. 2 of the as-filed specification demonstrates that RTS,S antigen in combination with a CpG oligonucleotide induces a low level antibody response. Comparison of the immune stimulatory effects of a CpG oligonucleotide with these different (but related) antigens illustrates the lack of predictability in determining appropriate adjuvants for particular antigens. These results emphasize that the efficacy of CpG oligonucleotides as adjuvants in a combination vaccine containing an RTS,S (or RTS,S*) antigen could not have been predicted with reliability as of the filing date of the subject application." (Remarks , p. 5)

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., antibody response; antibody titer; superior immune response) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to the comparison of Davis et al's HBsAg and CpG and Applicants' RTS,S antigen and CpG, it is noted that the claims are not directed to RTS,S and CpG. Therefore this is not a real side-by-side comparison. The claimed invention must have an antigen and 2 adjuvants (CpG and aluminum salt). It is noted that Example 1 of Davis et al also teaches that the administration of a composition comprising antigen (HBsAg) and 2 adjuvants (alum and CpG) to a subject yields an antibody titer of 500-fold higher than the preimmune serum and that the combination of adjuvants has a synergistic effect such that the immune response (i.e. antibody titer) is higher when both adjuvants are used (see Davis et al, col. 37, l. 10-17; col. 8). It would have been obvious to use the specific malarial antigens, RTS,S with more than one adjuvant as taught by Davis et al for the expected benefit of increasing the immune response or raising an immune response. Davis et al teaches that "[O]f even greater interest is the strong synergistic response when CpG ODN and alum are used together as adjuvants. This could allow better immune responses with lower or fewer doses of antigen." (col. 38, l. 8-12)

Further, even if a reference discloses an inoperative device, it is prior art for all that it teaches." Beckman Instruments v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). Therefore, "a non-enabling

reference may qualify as prior art for the purpose of determining obviousness under 35 U.S.C. 103." Symbol Techs. Inc. v. Opticon Inc., 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Applicants have asserted that it is impossible to predict with any certainty which combinations of adjuvants produce a superior immune response. However, as previously stated Davis et al teaches that the combination of adjuvants of CpG and alum are synergistic in nature and allow for a better immune response (col. 38). Davis et al teaches administering a composition (antigen, CpG and one non-nucleotidic adjuvant (alum)) in order to induce a stronger Th1 immune response than either the adjuvant or oligonucleotide produces alone (col. 3; cols. 6-7) .

It is the Examiner's position that the combination of references Stoute et al in view of Davis et al teach the claimed compositions for raising an immune response as well as methods of prevention or amelioration of plasmodium infection in a patient. A parasitic antigen would encompass a malarial antigen. As previously stated, the combination of adjuvants can be used with an antigen to mount an antigen specific immune response that is capable of reducing the level of or eradicating the infectious pathogen. An infectious disease, as used herein, is a disease arising from the presence of a foreign microorganism in the body." (Davis,

col. 8) It would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare a composition comprising the RTS,S and adjuvant (CpG or CpG and aluminum salts) since the prior art teaches that the RTS,S was a better vaccine composition when a combination of adjuvants were present. Further, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the CpG adjuvant in a vaccine composition for administration to a human since the art teaches that the CpG is a potent adjuvant and that it induces a Th1-type immune response, including Th1 cytokines such as IL-12 and interferon gamma for protection against various pathogens including parasites. It would have been obvious to a person of ordinary skill in the art at the time the invention was made that there would be a reasonable expectation of success of preventing or ameliorating plasmodium infection in a patient if the prepared composition taught by Stoute et al taken with Davis et al were administered to the patient. Further it is noted that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
April 29, 2007